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# Visual and Anatomic Outcomes in Patients with Diabetic Macular Edema with Limited Initial Anatomic Response to Ranibizumab in RIDE and RISE

*Dante J. Pieramici, MD,*[1] *Pin-wen Wang, PhD,*[2] *Beiying Ding, PhD,*[2] *Shamika Gune, MD*[2]

***Purpose:*** To explore the visual acuity and anatomic outcomes over 24 months of patients with diabetic macular edema (DME) who showed a delayed anatomic response after 3 ranibizumab injections in the RIDE and RISE trials.

***Design:*** Analysis of data from RIDE and RISE, 2 phase III, parallel, randomized, multicenter, double-masked trials (ClinicalTrials.gov identifiers, NCT00473382 and NCT00473330).

***Participants:*** Patients with DME (n = 681) who received monthly intravitreal ranibizumab 0.3-mg injections, ranibizumab 0.5-mg injections, or sham injections.

***Methods:*** Patients were separated into 3 groups: delayed responders (ranibizumab-treated patients with ≤10% central foveal thickness [CFT] reduction after 3 injections), immediate responders (ranibizumab-treated patients with >10% CFT reduction after 3 injections), and sham recipients. Central foveal thickness was measured by time-domain optical coherence tomography, best-corrected visual acuity (BCVA) was measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores, and diabetic retinopathy (DR) was measured by the standardized ETDRS severity scale (using fundus photographs).

***Main Outcome Measures:*** Month-24 CFT, BCVA, and DR severity levels.

***Results:*** In RIDE and RISE, 9% to 10% of ranibizumab-treated eyes were delayed responders. At month 24, delayed responders had less CFT reduction (median, −102 μm) from baseline compared with immediate responders (median, −274 μm; $P < 0.0001$). Delayed responders gained a median of 10 letters at 24 months, similar to immediate responders (14 letters; $P = 0.15$). At month 24, DR improvement among the delayed responders (31% and 22% of patients with ≥2- or ≥3-step DR improvement, respectively) was comparable with that among immediate responders (42% and 17%, respectively; $P = 0.21$ and $P = 0.48$, respectively).

***Conclusions:*** With continued treatment, at month 24, patients with DME with delayed anatomic response (≤10% CFT reduction) after 3 ranibizumab injections had visual acuity gains and DR improvement similar to those of patients with DME who had immediate anatomic response. *Ophthalmology 2016;123:1345-1350 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

The treatment paradigm for diabetic macular edema (DME) has changed dramatically in recent years.[1–3] With the various treatment options, clinicians must determine when a patient has failed one treatment and when to switch to another. A retrospective claims analysis (2008–2011) of patients newly diagnosed with retinal vein occlusion or DME revealed that patients with DME received an average of 2.2 to 3.6 bevacizumab injections annually,[4] markedly fewer than the number received by patients in major clinical trials of ranibizumab. These findings suggest that anti–vascular endothelial growth factor (VEGF) therapy is underused in the treatment of DME and also raise the question of when to designate a patient as nonresponsive to anti-VEGF treatment.

The RIDE and RISE trials (ClinicalTrials.gov identifiers, NCT00473382 and NCT00473330) were 2 phase III, parallel, randomized, multicenter, double-masked trials in which patients with DME received monthly intravitreal ranibizumab 0.3-mg injections, ranibizumab 0.5-mg injections, or sham injections. These studies were sham controlled for the first 2 years; in the third year, patients in the sham group could cross over to receive ranibizumab 0.5 mg monthly. Visual acuity and anatomic improvements generally were seen in ranibizumab-treated patients as early as 7 days after the first injection and were maintained over 3 years.[5,6]

The objective of this analysis was to answer the following clinical questions: When is it appropriate to say that a patient has failed to respond to anti-VEGF treatment? If a patient does not respond initially, does that mean they will never respond? Our study explored the visual acuity, optical coherence tomography (OCT), and diabetic retinopathy (DR) outcomes over 24 months in patients with DME (n = 681) who had little or no immediate anatomic



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response after 3 ranibizumab injections in the phase III RIDE and RISE trials.

## Methods

The methods of RIDE and RISE have been described previously in detail.[5,6] These trials complied with the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. Protocols were approved by institutional review boards or ethics committees, and written informed consent was obtained from all patients before study entry.

This analysis was limited to data at month 24, before the sham recipients crossed over to ranibizumab. All patients were separated into 3 responder status groups based on their treatment arm and central foveal thickness (CFT) change from baseline after 3 injections of ranibizumab: delayed responders (ranibizumab-treated patients with ≤10% CFT reduction), immediate responders (ranibizumab-treated patients with >10% CFT reduction), and sham recipients. The 3-injection cutoff was selected because after 3 doses (which can be considered loading doses), patients were eligible for laser treatment. Because one of the criteria for laser treatment was CFT of 250 μm or more with a less than 50-μm reduction from the prior month's measurement, reliable interpretation of the data is challenging after 3 doses because of the confounding effect of laser treatment. Overall, 20% to 39% of ranibizumab-treated patients and 70% to 74% of sham-treated patients received macular laser treatment, and 0% to 1.6% of ranibizumab-treated patients and 11% to 12% of sham-treated patients received panretinal photocoagulation laser in the RIDE and RISE studies at 24 months.[5]

Methodology for measuring anatomic outcome of CFT on time-domain OCT, best-corrected visual acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, and DR by the standardized ETDRS severity scale (using fundus photographs) was the same as described previously.[5] Analyses were based on observed data without imputation for missing values. Descriptive summaries by responder status were generated at baseline and month 24. Data were analyzed by medians and interquartile ranges because of the small sample sizes of delayed responders. The Kaplan-Meier survival method was used to estimate the median time to first anatomic response (>10% CFT reduction). The Wilcoxon rank-sum test was used to compare between the responder groups the distribution of continuous CFT, BCVA, and DR end points at baseline and month 24. The proportions of patients with CFT of 250 μm or less at baseline and month 24, 10-letter or more loss at month 24, and 2- or 3-step DR improvement at month 24 were compared between responder groups using the Fisher exact test.

## Results

Overall, in the RIDE and RISE trials, the median time to first anatomic response was 9 days for ranibizumab-treated patients. After 3 injections, 10% (23/224) of the ranibizumab 0.3-mg group and 9% (21/229) of the ranibizumab 0.5-mg group were delayed responders (≤10% CFT reduction). The delayed responder group was compared with the entire sham group (n = 228).

### Baseline Characteristics

At baseline, delayed responders had thinner retinas (median, 397 μm) compared with immediate responders (median, 459 μm; $P = 0.002$) and with sham recipients (median, 460 μm; $P = 0.01$; Fig 1A). Overall, less than 10% of patients had CFT of 250 μm or less at baseline: 9.1% (4/44) of delayed responders, 4.0% (16/405) of immediate responders, and 6.4% (14/220) of sham recipients.

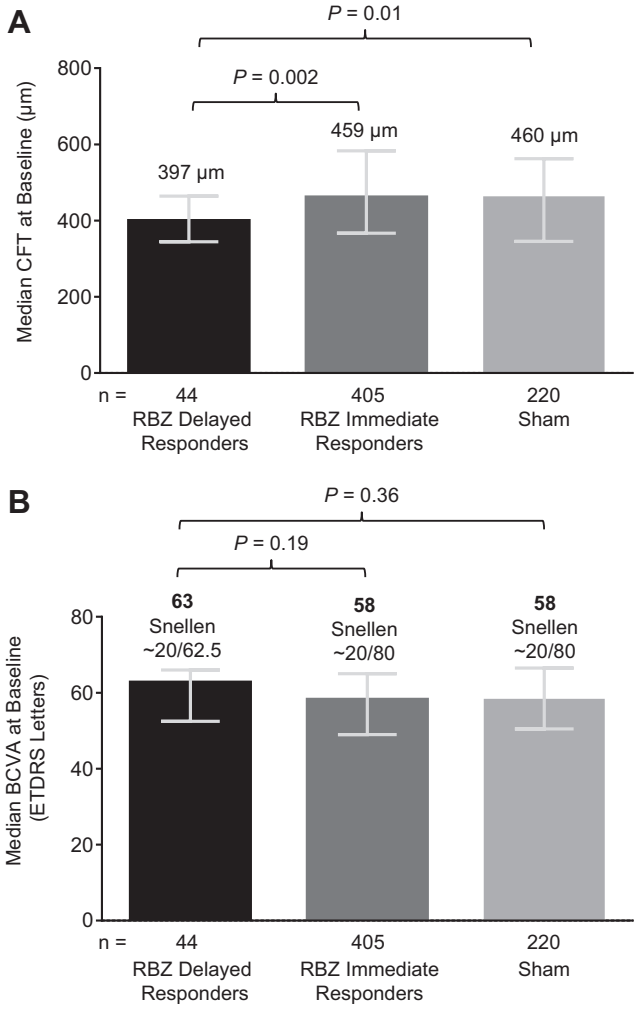


**Figure 1.** Bar graphs showing baseline values of (**A**) median central foveal thickness (CFT) and (**B**) median best-corrected visual acuity (BCVA) among the ranibizumab (RBZ)-treated delayed responders (≤10% CFT reduction after 3 injections), RBZ-treated immediate responders (>10% CFT reduction after 3 injections), and sham-treated patients. Data are from time-domain optical coherence tomography images and include patients treated with RBZ 0.3 or 0.5 mg. Error bars are lower and upper quartiles. The Wilcoxon rank-sum test was used to compare between responder groups. ETDRS = Early Treatment Diabetic Retinopathy Study.

Numerically, a greater proportion of delayed responders had CFT of 250 μm or less at baseline, compared with immediate responders and sham recipients, but the difference was not statistically significant ($P = 0.12$ and $P = 0.51$, respectively).

At baseline, delayed responders had BCVA comparable to that of immediate responders and sham recipients (median, 63, 58, and 58 ETDRS letters, respectively; Snellen equivalent, approximately 20/62.5, approximately 20/80, and approximately 20/80, respectively; $P = 0.19$ vs. immediate responders; $P = 0.36$ vs. sham recipients; Fig 1B).

At baseline, there were no statistically significant differences in DR severity level between immediate responders and delayed responders overall ($P = 0.16$; Table 1). However, a greater proportion of delayed responders had only mild or moderate nonproliferative DR (22.7% and 22.7%, respectively) at baseline, compared with immediate responders (13.9% and 11.8%, respectively) and sham recipients (15.1% and 13.7%, respectively).

Table 1. Diabetic Retinopathy Severity Levels at Baseline

| DR Severity Level | Delayed Responders (n = 44) | Immediate Responders (n = 397) | Sham (n = 219) |
|---|---|---|---|
| 10, 12 (DR absent) | 0 (0) | 2 (0.5) | 1 (0.5) |
| 14A–14C, 14Z, 15, 20 (DR questionable) | 1 (2.3) | 3 (0.8) | 3 (1.4) |
| 35A–35F (mild NPDR) | 10 (22.7) | 55 (13.9) | 33 (15.1) |
| 43A–43B (moderate NPDR) | 10 (22.7) | 47 (11.8) | 30 (13.7) |
| 47A–47D (moderately severe NPDR) | 6 (13.6) | 120 (30.2) | 61 (27.9) |
| 53A–53E (severe NPDR) | 2 (4.6) | 19 (4.8) | 11 (5.0) |
| 60, 61A, 61B (mild PDR) | 14 (31.8) | 114 (28.7) | 54 (24.7) |
| 65A–65C (moderate PDR) | 1 (2.3) | 12 (3.0) | 11 (5.0) |
| 71A–71D (high-risk PDR) | 0 (0) | 4 (1.0) | 2 (0.9) |
| 75 (high-risk PDR) | 0 (0) | 1 (0.3) | 0 (0) |
| Missing/cannot grade | 0 (0) | 20 (5.0) | 13 (5.9) |

DR = diabetic retinopathy; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.
Data are no. (%). The Wilcoxon rank-sum test was used to compare ranibizumab immediate responders and delayed responders ($P = 0.16$).

### Optical Coherence Tomography Outcomes

At month 24, delayed responders had less CFT reduction (median, −102 μm) from baseline compared with immediate responders (median, −274 μm; $P < 0.0001$) and CFT reduction comparable to that of sham recipients (median, −153 μm; $P = 0.33$; Fig 2A). At month 24, delayed responders had thicker retinas compared with immediate responders (median, 209 vs. 157 μm, respectively; $P < 0.0001$); median CFT was comparable between delayed responders and sham recipients (median, 244 μm; $P = 0.26$). At month 24, a smaller proportion of delayed responders (65.8%) had CFT of 250 μm or less compared with immediate responders (82.8%; $P = 0.02$); the proportion was similar to that of the sham group (51.7%; $P = 0.15$).

### Visual Outcomes

At month 24, delayed responders and immediate responders had comparable BCVA gain from baseline (median, 10 vs. 14 letters; $P = 0.15$); delayed responders had greater BCVA gain compared with sham recipients (median, 5 letters; $P = 0.002$; Fig 2B). Both ranibizumab responder groups had a median BCVA of 73 ETDRS letters (Snellen equivalent, approximately 20/40; $P = 0.58$) at month 24; sham recipients had a median BCVA of 65 ETDRS letters (Snellen equivalent, approximately 20/50; $P = 0.001$ vs. delayed responders; Fig 2B). A similar proportion of delayed and immediate responders gained 2 lines or more of vision (62.5% vs. 68.0%, respectively; $P = 0.48$) at month 24; a smaller proportion of the sham group gained 2 lines or more (33.0%) compared with the delayed responders ($P = 0.001$). Comparable findings were seen for 3-line or more gain at month 24; a similar proportion of delayed and immediate responders gained 3 lines or more of vision (35.0% vs. 46.8%, respectively; $P = 0.18$), and a smaller proportion of the sham group gained 3 lines or more (18.9%; $P = 0.03$ vs. delayed responders). At month 24, the proportions of patients with 10-letter or more loss were low and comparable between immediate responders (3.2%) and delayed responders (5.0%; $P = 0.63$). A numerically greater proportion of sham-treated patients (13.5%) lost 10 letters or more at month 24 ($P = 0.18$ vs. delayed responders).

### Diabetic Retinopathy Outcomes

The proportions of patients with 2-step or more or 3-step or more DR improvement at month 24 were comparable between immediate and delayed responders ($P = 0.21$ and $P = 0.48$, respectively; Fig 3). A significantly larger proportion of delayed responders had 2-step or more or 3-step or more DR improvement compared with the sham group ($P = 0.0003$ and $P < 0.0001$, respectively) at month 24 (Fig 3).

## Discussion

Few ranibizumab-treated eyes (9% to 10%) in RIDE and RISE were delayed responders (≤10% CFT reduction after 3 injections). At 24 months, delayed responders had less CFT reduction from baseline compared with immediate responders. Despite little or no immediate anatomic response, significant visual acuity improvement occurred with continued treatment. Continuing treatment did not result in visual loss; very few ranibizumab-treated patients (5%) lost 10 or more ETDRS letters. These delayed responders gained a median of 10 letters at 24 months, similar to immediate responders (14 letters). At month 24, there was also DR improvement among the delayed responders (31% and 22% of patients with ≥2- or ≥3-step DR improvement, respectively), which was comparable with immediate responders (42% and 17%, respectively). Our study demonstrated that certain patients may be slow to respond anatomically, but still can experience vision gains and DR improvement over 24 months with continued ranibizumab therapy. Our analysis focused on anatomic response because generally, in clinical practice, decision making regarding treatment is in large part based on OCT changes. However, our findings reaffirm the discordance between retinal thickness and visual acuity.[7] Many other retinal anatomic details that may predict the potential of recovery are likely not captured in a summary measurement such as CFT.

To further investigate potential reasons for the comparatively decreased anatomic improvement in the delayed responders group, we considered differences in baseline OCT. Delayed responders had a median baseline CFT less than 400 μm, whereas immediate responders had a median baseline CFT more than 400 μm. One hypothesis is that the delayed responders had less of an anatomic response compared with immediate responders because of a floor effect; that is, patients who started with thinner CFTs did not have excess fluid to lose. However, we found that none of the delayed responders had CFT 170 μm or less after 3 injections. In addition, in an analysis adjusting for baseline

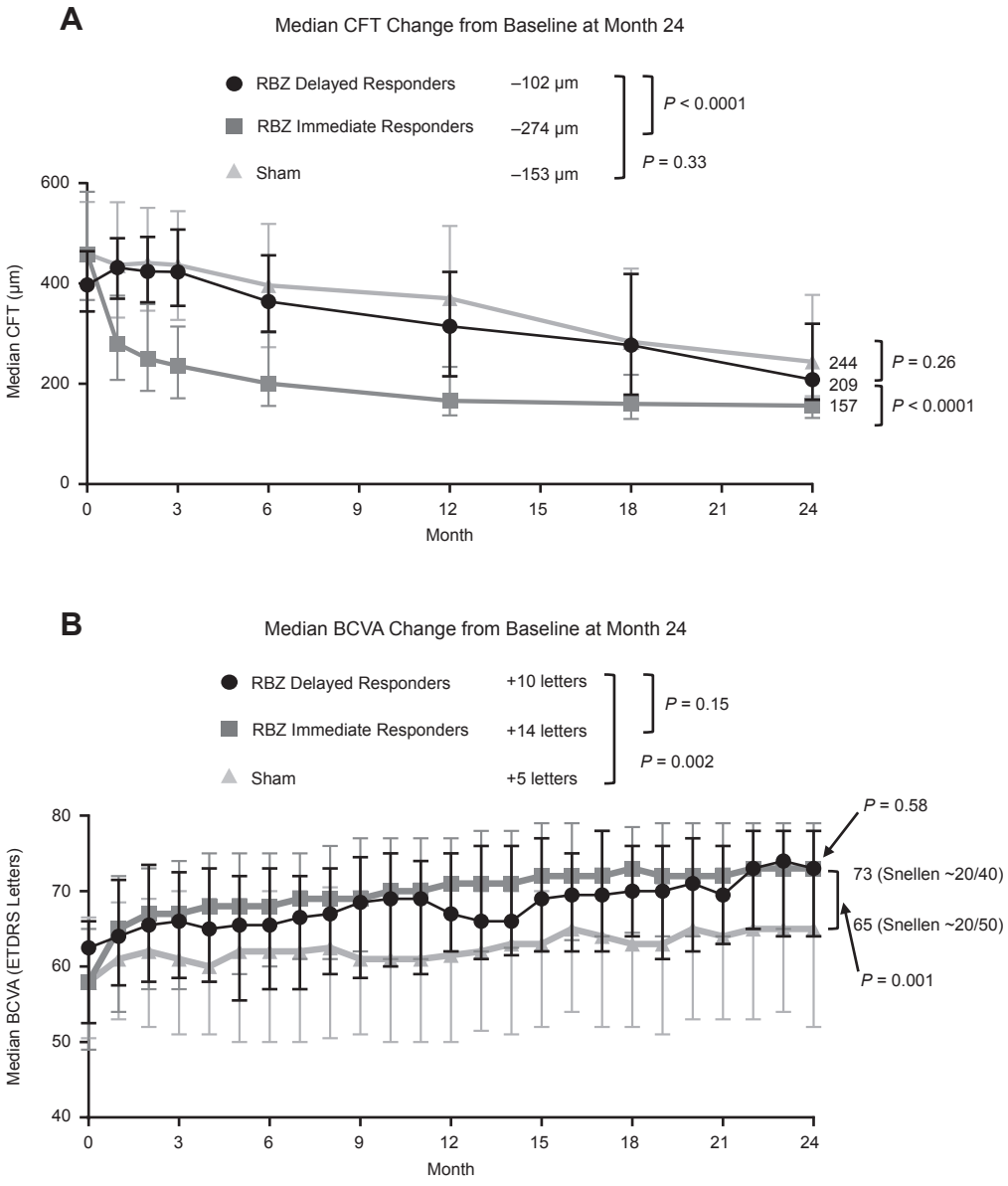


**Figure 2.** Graphs showing the change from baseline over 24 months in (**A**) median central foveal thickness (CFT) and (**B**) median best-corrected visual acuity (BCVA) among the ranibizumab (RBZ)-treated delayed responders (≤10% CFT reduction after 3 injections), RBZ-treated immediate responders (>10% CFT reduction after 3 injections), and sham-treated patients. Data are from time-domain optical coherence tomography images and include patients treated with RBZ 0.3 or 0.5 mg. Error bars are lower and upper quartiles. The Wilcoxon rank-sum test was used to compare between responder groups. At month 24, for CFT, n is 38, 338, and 176, and for BCVA, n is 40, 344, and 185, for RBZ delayed responders, RBZ immediate responders, and sham recipients, respectively. ETDRS = Early Treatment Diabetic Retinopathy Study.

CFT thickness, visual and anatomic results were similar to our main analysis and were not included in this article. The delayed responders experienced visual improvement despite limited anatomic response; this functional response may be the result of other positive effects of anti-VEGF therapy on the diabetic retina besides reduction in edema. For example, analysis of the RIDE and RISE study data demonstrated that ranibizumab treatment improved DR severity and prevented worsening in patients with DME.[8,9] Further research is warranted to explore the physiologic processes behind the delayed anatomic response to anti-VEGF treatment in patients with DME.

Studies have examined whether other baseline characteristics affect treatment outcome with anti-VEGF therapy in DME. For instance, other studies have found that patients with focal DME[10] or greater baseline subfoveal choroidal thickness[11] may have more potential for visual acuity improvement. In our study, the delayed responders tended to have significantly thinner retinas, slightly better BCVA, and more mild DR severity at baseline, suggesting that these patients had more mild disease to begin with. In a retrospective case series (n = 175 eyes),[12] patients with central retinal thickness (CRT) more than 400 µm at baseline had a greater anatomic response to bevacizumab

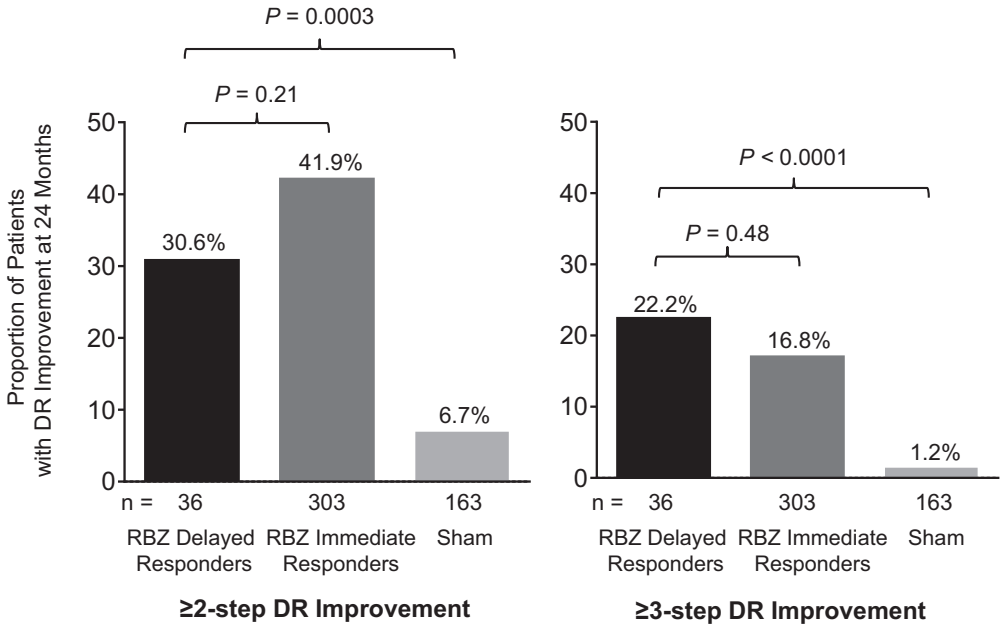


**Figure 3.** Bar graphs showing the proportion of patients with 2-step or more or 3-step or more improvement in diabetic retinopathy (DR) at month 24. Data include patients treated with ranibizumab (RBZ) 0.3 or 0.5 mg. The Fisher exact test was used to compare RBZ immediate responders and delayed responders and to compare RBZ delayed responders and sham recipients.

treatment in a real-world setting; as expected, these patients may have more room for improvement in terms of OCT reduction. Similar to our findings, both groups (baseline CRT, <400 and >400 μm) had significant vision improvement, and there was no clear difference between groups in terms of vision gains. Likewise, in another study (n = 854 eyes) evaluating ranibizumab 0.5 mg plus prompt or deferred laser treatment or triamcinolone 4 mg plus prompt laser treatment for DME,[13] patients with baseline central subfield thickness less than 400 μm experienced less OCT reduction than those with baseline central subfield thickness of 400 μm or more, but there were no clinically important differences in BCVA at 1 year between the 2 subgroups. In contrast, in the RESTORE study (n = 345) comparing laser monotherapy with ranibizumab 0.5-mg monotherapy (3 monthly loading doses, then as-needed injections) or combined with laser treatment,[14] patients with CRT more than 400 μm at baseline had greater gains in BCVA from baseline compared with those who had baseline CRT 300 to 400 μm or less than 300 μm.

It should be noted that DME is a complex disease, and as such, there are a number of other factors that could impact response to anti-VEGF therapy. Although generally elevated in patients with DME compared with patients without, levels of VEGF have been observed to be highly variable in the vitreous of different patients.[15] Furthermore, there is an upregulation of a multitude of growth factors and cytokines that contribute to the breakdown of the blood−retinal barrier and consequent vascular leakage responsible for DME, including angiopoietins, tumor necrosis factor, interleukins, and matrix metalloproteinases.[2] Therefore, it is unsurprising that a variability in patient response to anti-VEGF therapy has been observed in several studies. The proportion of ranibizumab-treated DME patients gaining 3 lines or more of BCVA was 37% to 51% in RIDE and RISE at 36 months[6] and 27% to 38% in Diabetic Retinopathy Clinical Research Network protocol I at 5 years.[16] Similarly, in the VISTA and VIVID studies, 31% to 38% of aflibercept-treated DME patients gained 3 lines or more of BCVA at week 100.[17] In a head-to-head comparison of aflibercept, bevacizumab, and ranibizumab for treatment of DME (Diabetic Retinopathy Clinical Research Network protocol T), the proportions of patients gaining 3 lines or more of BCVA were 42%, 29%, and 32%, respectively.[18] As such, it is most often the case that less than 50% of patients show 3 lines or more of visual acuity improvement in studies of anti-VEGF therapy.

With continued treatment, delayed responders (≤10% CFT reduction after 3 ranibizumab injections) had month-24 outcomes that were similar to those seen in immediate responders (>10% CFT reduction); delayed responders gained an average of 10 letters, and up to 30% had a 2-step or more or 3-step or more improvement. Data from this analysis support continuing ranibizumab therapy for DME even when patients have delayed anatomic responses to treatment.

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[1] California Retina Consultants, Santa Barbara, California.

[2] Genentech, Inc., South San Francisco, California.

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B.D.: Employee — Genentech, Inc., South San Francisco, California

S.G.: Employee — Genentech, Inc., South San Francisco, California

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Conception and design: Pieramici

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Abbreviations and Acronyms:
**BCVA** = best-corrected visual acuity; **CFT** = central foveal thickness; **CRT** = central retinal thickness; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **OCT** = optical coherence tomography; **VEGF** = vascular endothelial growth factor.

Correspondence:
Dante J. Pieramici, MD, California Retina Consultants, 515 East Micheltorena Street, Suite C, Santa Barbara, CA 93103. E-mail: dpieramici@yahoo.com.